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(54) Title: RUTHENIUM COMPLEXES AND THEIR USE IN ASYMMETRIC HYDROGENATION
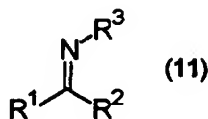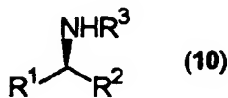
(57) **Abstract:** A process for the preparation of an enantiomerically enriched chiral amine of formula (10), or the opposite enantiomer thereof, from an imine of formula (11) wherein (i) R^1 is aryl, R^2 is alkyl and R^3 is aryl or aryl-CH_2-, or (iii) R^2 is linked with R^1 and/or R^3 to form one or more rings and R^3 or R^1 (if not in a ring) is H or a non-interfering organic group, the number of C atoms in each of R^1, R^2 and R^3 being up to 30, comprises asymetric hydrogenation of the imine in the presence of a base and, as catalyst, a ruthenium complex of a chiral diphosphine and a chiral diamine.

RUTHENIUM COMPLEXES AND THEIR USE IN ASYMMETRIC HYDROGENATION

Field of the Invention

       This invention relates to ruthenium complexes bearing a chiral diphosphine and a chiral diamine and their use as catalysts for the asymmetric hydrogenation of imines.

       In this context and throughout the following text, the term "catalyst(s)" refers to the isolated pre-catalyst that is added to the reaction vessel for hydrogenation and which typically undergoes a change in composition *in situ* to generate one or more catalytically active species.

Background of the Invention

       Although many highly enantioselective chiral catalysts are available for the asymmetric hydrogenation of C=C and C=O bonds, relatively few exist for effective reduction of the analogous C=N function. The production of chiral amines *via* this methodology still represents a major challenge. In the past ten years, progress in this field has been made with catalysts based on complexes of rhodium, iridium, ruthenium and titanium, with most recent emphasis being devoted to Ir and Ti.

       A recent review provides a comprehensive summary of the most important advances in this field (Kobayashi and Ishitani, *Chem. Rev.*, **1999**, *99*, 1069); representative examples include those detailed below. Osborn and co-workers developed chiral Ir complexes of the type [Ir(P-P)HI$_2$]$_2$ (**1**), in which (P-P) represents a chiral ligand, and analogues thereof; see Chan and Osborn, *J. Am. Chem. Soc.*, **1990**, *112*, 9400; Chan *et al.*, *J. Chem. Soc., Chem. Commun.*, **1990**, *869*; Sablong and Osborn, *Tetrahedron Lett.*, **1996**, *37*, 4937. Although these systems showed reasonable activities, the enantioselectivites were in general only moderate, despite employing various chiral diphosphines (e.g. up to 35% ee for the cyclic imine **2**). Spindler *et al.* independently reported an *in situ* prepared Ir catalyst incorporating JOSIPHOS (**3**) as the chiral ligand, and subsequently applied it to the industrial production of (*S*)-Metolachlor (**4**) (Spindler *et al.*, *Angew. Chem., Int. Ed. Engl.*, **1990**, *29*, 558; Blaser and Spindler, *Topics in Catalysis*, **1997**, *4*, 275).
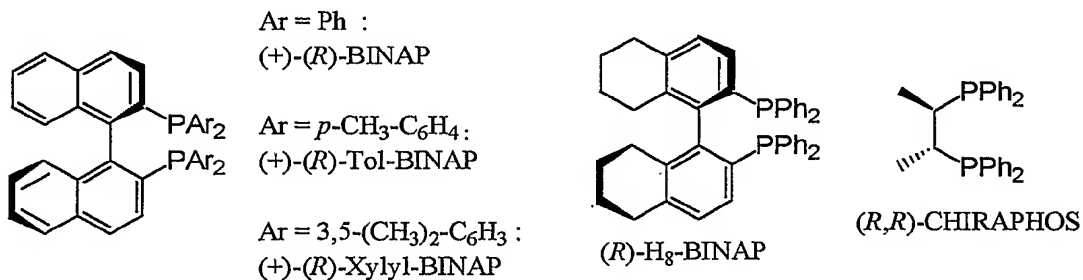
(1)   **(2)**   **(3)**   **(4)**
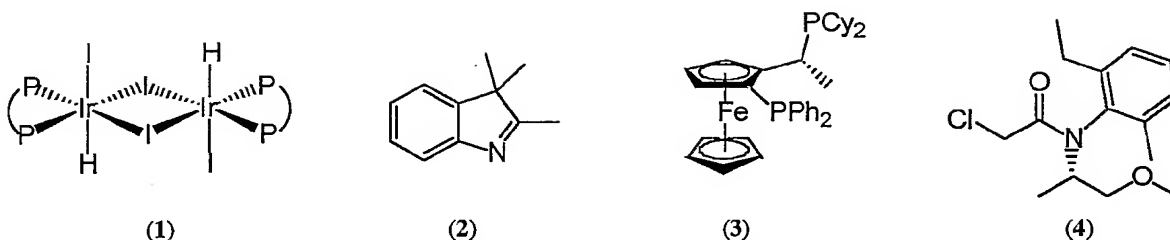
Buchwald and co-workers have prepared chiral titanocene complexes **5** and **6**, and have effectively employed them in reductive amination of a range of imines (Willoughby and Buchwald, *J. Am. Chem. Soc.*, **1992**, *114*, 7562; *J. Am. Chem. Soc.*, **1994**, *116*, 8952;

5   *J. Am. Chem. Soc.*, **1994**, *116*, 11703). These catalysts are effective in both asymmetric hydrogenation and asymmetric hydrosilylation processes, although their practical utility is limited by (a) the requirement for high operating pressures (typically >60 bar H_2) in the former and (b) the requirement to activate the catalyst in the reaction vessel by addition of butyl-lithium and phenyl silane. More recently, Pfaltz and co-workers have employed

10   an Ir phosphine-oxazolidine complex (**7**) for the asymmetric hydrogenation of various prochiral imines. Although *N*-(phenylethylidene)aniline was successfully reduced in 99% yield with 89% ee, the use of cyclic imines as substrates resulted in much lower enantioselectivities (Schnider *et al.*, *Chem. Eur. J.*, **1997**, *3*, 887). Lastly, Bianchini *et al.* have addressed the asymmetric hydrogenation of 2-methylquinoxaline (**8**), which is

15   challenging due to the aromatic nature of the substrate (Bianchini *et al.*, *Organometallics*, **1998**, *17*, 3308). Ee's of up to 90% (at 54% substrate conversion) were achieved using the orthometalated dihydride complex (**9**) as catalyst, although at 96.5% substrate conversion the ee decreased to 73%.
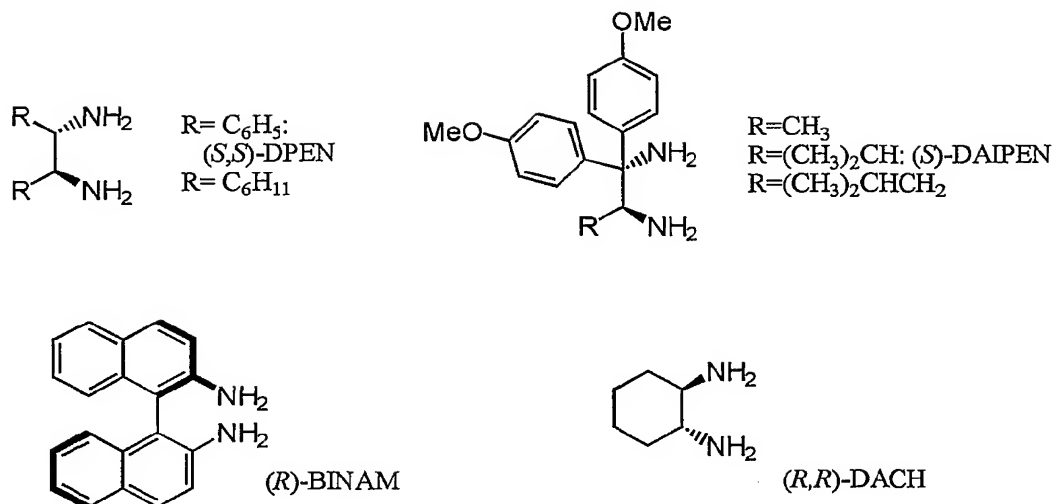
20

    (5) X =F
    (6) X-X =

    (7)

25   **(8)**   **(9)**

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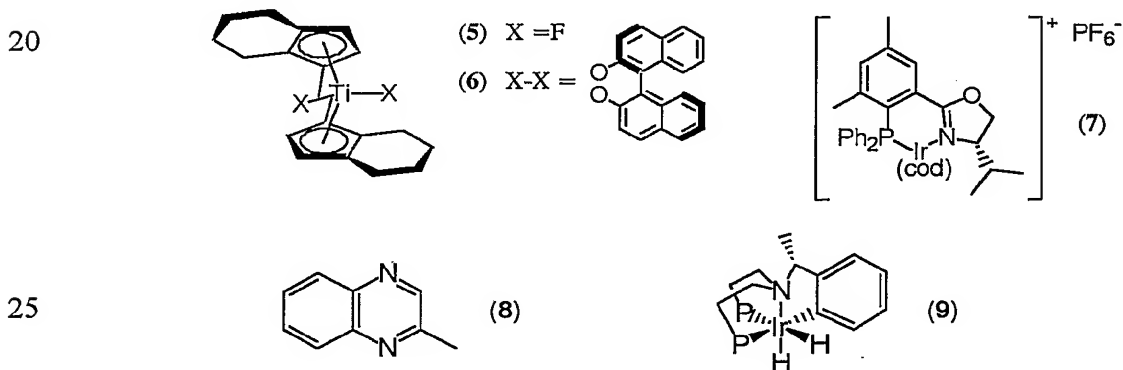
After the date of the present invention, Abdur-Rashid *et al*, in *Organometallics* **2001**, *21*, 1047, disclosed that RuHCl (diphosphine) (diamine) complexes catalyse the hydrogenation of imines. The disphosphine ligands that were used are BINAP and DPPACH. The imine substrates were all acylic. It is unclear what of this paper was 5   published, at a conference in May 2000.

Despite the successful examples cited above, there remains a need to identify a general class of structurally related catalysts that are chemically robust and give high activity and enantioselectivity in the asymmetric hydrogenation of a broad range of imine substrates, both cyclic (including aromatic imines) and acyclic. For commercial 10   applications, an important requirement of such a class of catalysts is the facility to readily vary individual components of the catalyst, especially the chiral ligand, such that for a given application the best match of substrate and catalyst can be identified by multi-well screening.

In the related field of catalytic asymmetric hydrogenation of ketones, Noyori *et al.* 15   have pioneered the use of ruthenium complexes bearing a diphosphine ligand and a diamine ligand. At least one and usually both of these ligands are chiral. Initial studies of these complexes, as reported in EP-A-0718265, demonstrated the highly efficient reduction of unfunctionalised aromatic ketones. Examples of chiral diphosphines employed were BINAP, Tol-BINAP, Xylyl-BINAP, H_8BINAP and CHIRAPHOS. 20   Examples of chiral diamines employed were DPEN, DAIPEN and others.

Ar = Ph :
(+)-(*R*)-BINAP

Ar = *p*-CH$_3$-C$_6$H$_4$:
(+)-(*R*)-Tol-BINAP

Ar = 3,5-(CH$_3$)$_2$-C$_6$H$_3$:
(+)-(*R*)-Xylyl-BINAP

(*R*)-H$_8$-BINAP

(*R,R*)-CHIRAPHOS

$R=C_6H_5$: (S,S)-DPEN
$R=C_6H_{11}$

$R=CH_3$
$R=(CH_3)_2CH$: (S)-DAIPEN
$R=(CH_3)_2CHCH_2$

(R)-BINAM

(R,R)-DACH

It was subsequently disclosed by R. Noyori and co-workers (Ohkuma *et al.*, J. *Am. Chem. Soc.*, **1995**, *107*, 2675 and 10417) that a fully characterised diphosphine-ruthenium-diamine complex could be isolated and used as the catalyst. In particular, high productivity and high selectivity were always associated with the use of the chiral biaryl-phosphines Tol-BINAP and Xylyl-BINAP and the chiral diamines DPEN and DAIPEN (Doucet *et al.*, *Angew. Chem. Int. Ed.* **1998**, *37*, 1703 and Ohkuma *et al.*, *J. Am. Chem. Soc.*, **1998**, *120*, 13529). Analogous catalysts incorporating the DuPHOS family of ligands have recently been prepared (Akotsi *et al.*, *Chirality*, **2000**, *12*, 514), although their application to the asymmetric hydrogenation of ketones or imines has not been reported.

R= Me: (S,S)-Me DuPHOS
R= Et: (S,S)-Et-DuPHOS
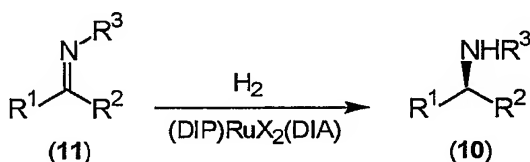R= i-Pr: (R,R)-i-Pr-DuPHOS
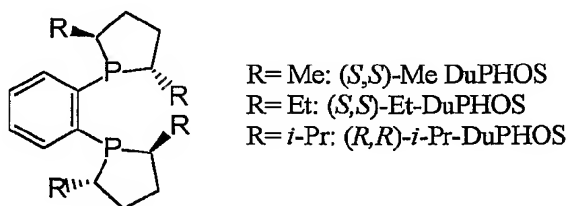
Summary of the Invention

According to the present invention, a ruthenium complex, bearing a chiral diphosphine and chiral diamine, is used in the asymmetric hydrogenation of a diverse range of prochiral imines. When in the presence of a base, such catalysts can be used to produce chiral amines with high to excellent enantioselectivites, in some cases better than those methods reported to date.

The present invention provides an effective means of accessing an enantiomerically enriched chiral amine of formula (10), or the opposite enantiomer thereof, from an imine of formula (11), according to the following reaction:


$$R^1 \overset{\overset{\displaystyle N^{-R^3}}{\|}}{\underset{(11)}{\diagup}} R^2 \xrightarrow[\text{(DIP)RuX}_2\text{(DIA)}]{H_2} R^1 \overset{\overset{\displaystyle NHR^3}{|}}{\underset{(10)}{\diagup}} R^2$$

wherein the catalyst is shown for the purpose of illustration, (i) R^1 is aryl, R^2 is alkyl and R^3 is aryl or aryl-CH_2-, or (ii) R^2 is linked with R^1 and/or R^3 to form one or more rings and R^3 or R^1 (if not in a ring) is H or a non-interfering organic group, the number of C atoms in each of R^1, R^2 and R^3 being up to 30. The novel process comprises asymmetric hydrogenation of the imine in the presence of a base and, as catalyst, a ruthenium complex of a chiral diphosphine and a chiral diamine.

Description of the Invention

In the illustrative reaction shown above, (DIP)RuX$_2$(DIA) represents the ruthenium complex that, following activation with base, catalyses the asymmetric hydrogenation process. DIP is a bis-tertiary phosphine in which the two phosphorus atoms are linked by a C_{2-7} carbon chain such that they form a 5-10 membered ring with the Ru atom, DIA is a diamine (typically vicinal) with any aromatic, alkyl or hydrogen substituent on the C_2-carbon chain linking the nitrogen atoms, and X is halide or carboxylate, preferably halide (Cl, Br, I or F) and more preferably chloride. Both DIP and DIA are chiral and substantially in the form of a single enantiomer.

In preferred embodiments of the present invention, DIP in the complex (DIP)RuX$_2$(DIA) is selected from one of two sub-classes of bis-tertiary phosphine. Firstly,

an atropisomeric bis-tertiary phosphine may be used, in which the two phosphorus atoms
are linked by a biaryl backbone. Representative members of this subclass include the
BINAP ligands depicted above, and ligands based on a biphenyl backbone, such as the
BIPHEP/BIPHEMP (respectively Y = OMe/Y = Me) series of formula (12), in which Ar

5   is a phenyl group optionally substituted with up to two alkyl groups and $(X)_n$ represents
one or more non-interfering substitutents. The second subclass of ligands are those in
which each phosphorus atom forms part of a four-membered (phosphetane) or five-
membered (phospholane) ring. The DuPHOS series of ligands are representative of this
subclass; in formula (13), R is C_{1-6} linear or branched alkyl and is preferably methyl or

10   ethyl.
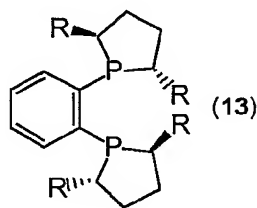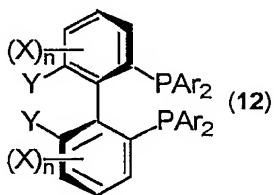
15

It will be understood by those of ordinary skill in the art that a formula such as (13)
represents the active nucleus of DuPHOS ligands and that it may be substituted without
affecting its function. Minor modifications may also be made to other ligands described

20   herein, to give functionally equivalent entities.

One class of imines that can be hydrogenated according to this invention is acyclic,
wherein R^1 is aryl, R^2 is alkyl and R^3 is aryl or aryl-CH_2-. For example, each aryl group
(which, for the purposes of this specification, includes heteroaryl) is phenyl optionally
substituted by one or more substituents having up to 6 C atoms, and R^2 is methyl or

25   another alkyl group of up to 6 C atoms. Representative acyclic substrates of this type are
N-(1-phenylethylidene)aniline and N-(1-phenylethylidene)benzylamine.

Another class of acyclic imines comprises those where R^1 and R^2 are linked to form
a ring; these substrates are acyclic because the C=N bond is not in a ring. A representative
example is N-(2,3-dihydro-1H-indan-2-ylidene)benzylamine.

30   Yet another class of imine substrates is cyclic, wherein R^2 and R^3 are linked to form
a ring, e.g. a cycloalkyl or heterocyclic ring (typically of 5 or 6 atoms) which may have a
fused benzene or other aromatic ring, or wherein R^1, R^2 and R^3 are linked. Any group

which is not in the cyclic imine ring, i.e. R^1, may be H or, for example, an alkyl or other group having up to 6 C atoms, but may be a bulkier hydrocarbon or other group provided that, as can readily be determined by one of ordinary skill in the art, it does not interfere in the hydrogenation reaction.

Representative cyclic substrates are dihydroquinolines and dihydroisoquinolines. The preferred ligand in the latter case at least is of the DuPHOS type.

Other representative cyclic substrates are indolenines, isoquinolines and quinoxalines. One preferred ligand type in such a case is biaryl, e.g. of the HexaPHEMP type (PCT/GB01/02467). These are of formula (12) wherein Y is CH_3, n is 2 and each X is CH_3, i.e. [4,4',5,5',6,6'-hexamethyl(1,1'-diphenyl)-2,2'-diyl]bis(diarylphosphine) ligands.

It will be appreciated that certain ligands may be preferred in conjunction with certain substrates. Thus, it is apparent from Examples 4-6 that the biaryl class of ligands may be better suited to cyclic imines whereas DuPHOS ligands work better with acyclic imines. In some cases, particular combinations give especially good results. However, a practitioner skilled in the art would recognise that any deviation from any trend would be evident on a case-by-case basis through a screening protocol, in which numerous combinations of ligand (DIP) and diamine (DIA) would be examined.

Also in preferred embodiments of the present invention, DIA in the complex $(DIP)RuX_2(DIA)$ is a diamine of formula (14), in which at least one of the amine-bearing centres is stereogenic, R_1, R_2, R_3 and R_4 are independently H, C_{1-20} alkyl or C_{6-20} aromatic, and any pair of R_1, R_2, R_3 and R_4 is optionally linked to form one or more rings.

$$H_2N\underset{H_2N}{\overset{R_1}{\diagdown}}\underset{R_3}{\overset{R_2}{\diagup}}R_4 \quad (14)$$
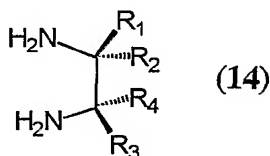
Compounds 15-19 and the opposite enantiomers are representative diamines. Another feature of the present invention is that, in certain cases, optimum performance of the catalyst is reliant on a given enantiomer of the DIP ligand being combined with the correct enantiomer of diamine. This matched-pair effect is evident for the use of DuPHOS ligands in Example 4 (compare entries 5 and 7 in the table following Example 4). Accordingly, the diamine (R,R)-DPEN is preferably combined with either (R,R)-methyl

DuPHOS or (R,R)-ethyl DuPHOS, and the matching of (S,S)-stereoisomers is likewise effective.

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(15): (R,R)-DPEN   (16)   (17): (R)-DAIPEN

10

(18): (R,R)-ANDEN   (19): (R,R)-DACH
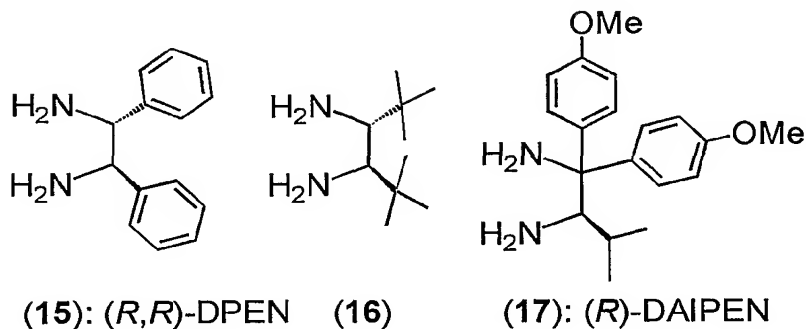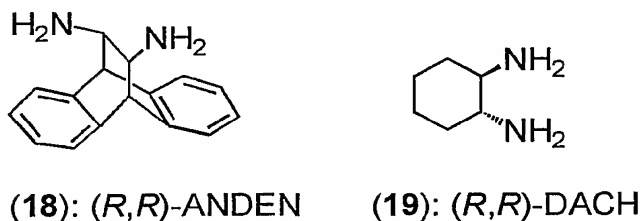
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Successful operation of the process of the present invention requires the presence of a base, preferably an alkali metal alkoxide, for example potassium t-butoxide or sodium diisoproproxide, which is easily separated from the product by standard extractive work-
20   up procedures. Most preferably, the base is potassium t-butoxide. The amount of base relative to the imine substrate is in the range of 0.01-2.0 molar equivalents and more usually is typically in the range of 0.05-1.0 molar equivalents. For certain imine substrates, especially those prone to isomerisation with respect to position of the C=N bond, it is advantageous to reduce the amount of base to around 0.05 equivalents or lower, in order
25   to achieve acceptable enantioselectivity. This effect is evident from Example 7 (below), for the ketimine (20). Control experiments, in the absence of catalyst, show facile equilibration of (20) to racemic aldimine (21) in the presence of 1.0 equivalent of potassium t-butoxide.   Aldimine (21) is also a hydrogenation substrate but such hydrogenation does not generate a chiral centre.

(20; E:Z = 11.4:1.0)   (21)
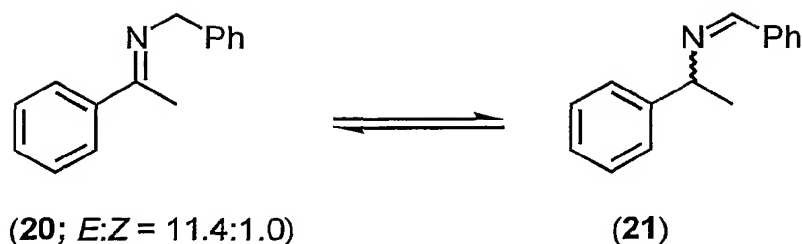
For operation of the present invention, other characteristic features of preferred embodiments are as follows:

i)   the reaction solvent is selected from isopropanol, ethanol, toluene, benzene, chlorobenzene and tetrahydrofuran; optionally, for liquid substrates (or solid substrates that melt below the reaction temperature), the solvent can be omitted.

ii)   when a solvent is used, the substrate concentration is at least 0.5 M and more preferably is at least 3 M, since raising the concentration can improve the rate of reaction and/or the extent of substrate conversion.

iii) the reaction temperature is in the range 10-100°C and, in order to achieve good substrate conversion, is normally at least 40°C.

iv)   the reaction pressure is in the range 1-100 bar and, in order to achieve good substrate conversion, is normally at least 5 bar.

In summary, the process of the present invention provides an effective means of preparing a wide range of enantiomerically enriched chiral amines. In order to be economically viable, it is important that enantiomeric enrichment of the amine (10) is at least 50% ee, and is preferably at least 80% ee, or higher. If necessary, any shortfall in ee can subsequently be corrected by formation and crystallisation of a suitable acid salt form of the amine with a chiral acid or with an achiral acid conferring a conglomerate properties or a favourable eutectic composition. For commercial operation of the process, it is also important to effect good conversion of substrate to product, of at least 80% conversion and preferably at least 90% conversion

The invention is further illustrated by the following Examples. Examples 1-3 relate to the synthesis of complexes, while Examples 4-8 relate to hydrogenation. More

10

particularly, the substrates used in Examples 4 and 7 are acyclic imines, while those used in Examples 5, 6 and 8 are cyclic.

Example 1: [(*R,R*)-Me-DuPHOS-RuCl₂-(*R,R*)-DPEN]

      [Ru(C₆H₆)Cl₂]₂ (150 mg, 0.30 mmol) and (*R,R*)-Me-DuPHOS (184 mg, 0.60

5   mmol) were placed in a Schlenk tube which was degassed and filled with nitrogen three times. Anhydrous, degassed DMF (3 mL) was then added and the reaction was heated at 100°C for 60 minutes to give a deep red/brown solution. The solvent was removed under vacuum. (*S,S*)-DPEN (127 mg, 0.60 mmol) was then added and the tube evacuated and filled with nitrogen a further three times. Anhydrous, degassed CH₂Cl₂ (4 mL) was added

10   and the reaction mixture was stirred for a further 60 minutes at room temperature. After removal of all volatiles *in vacuo*, the residue was suspended in Et₂O (5 mL), filtered, and the filtrate evaporated to dryness to yield a tan-coloured solid. ³¹P NMR: 93.4 ppm (s). This tan solid residue is a suitable catalyst for the hydrogenation of imines.
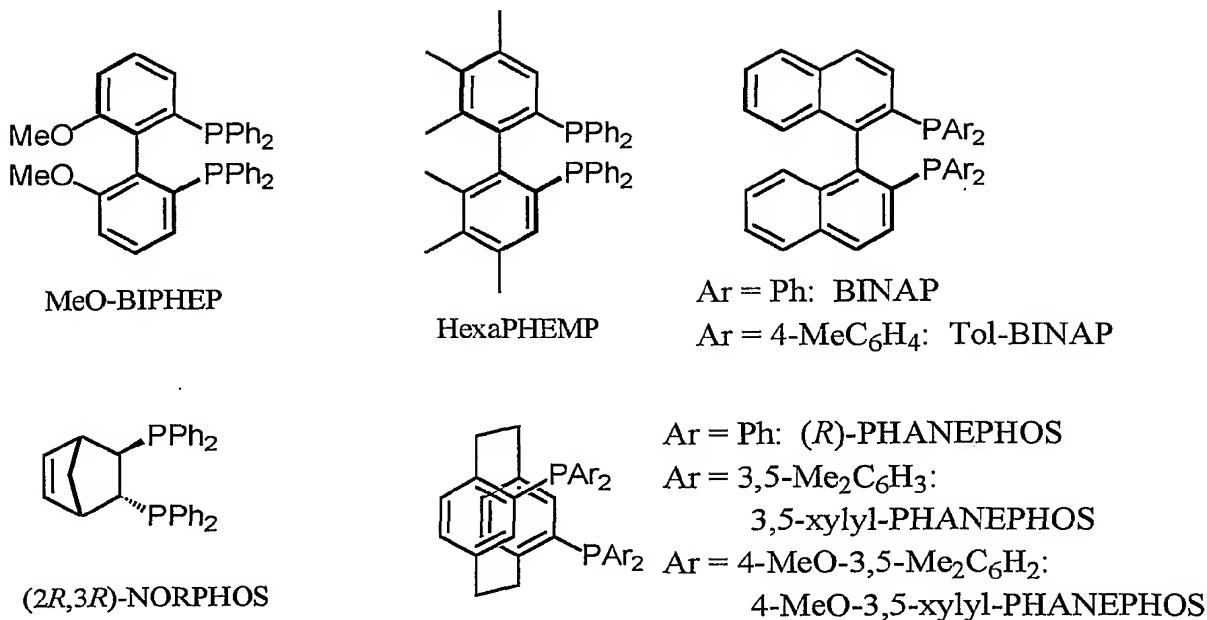
Example 2: [(*R,R*)-Et-DuPHOS-RuCl₂-(*R,R*)-DPEN]

15   [(*R,R*)-Et-DuPHOS-RuCl₂-(*R,R*)-DPEN] was prepared as described above for [(*R,R*)-Me-DuPHOS-RuCl₂-(*R,R*)-DPEN] using (*R,R*)-Et-DuPHOS. ³¹P NMR: 91.1 ppm (s).

Example 3: [(*R,R*)-*i*-Pr-DuPHOS-RuCl₂-(*S,S*)-DPEN]

      [(*R,R*)- *i*-Pr-DuPHOS-RuCl₂-(*S,S*)-DPEN] was prepared as described above for

20   [(*R,R*)-Me-DuPHOS-RuCl₂-(*R,R*)-DPEN] using (*R,R*)- *i*-Pr-DuPHOS and (*S,S*)-DPEN.

      Other catalysts shown in the tables in Examples 4-8 were prepared similarly. Ligands used in the preparation of catalysts are selected from those identified above and from the following:

MeO—BIPHEP

HexaPHEMP

Ar = Ph: BINAP

Ar = 4-MeC$_6$H$_4$: Tol-BINAP

(2R,3R)-NORPHOS

Ar = Ph: (R)-PHANEPHOS

Ar = 3,5-Me$_2$C$_6$H$_3$:

    3,5-xylyl-PHANEPHOS

Ar = 4-MeO-3,5-Me$_2$C$_6$H$_2$:

    4-MeO-3,5-xylyl-PHANEPHOS

<u>Typical general procedure for hydrogenation</u>

Hydrogenations were carried out in 50 mL Parr hydrogenation vessels (or a Baskerville multi-welled hydrogenation vessel) equipped with an injection port with a rubber septum for the addition of the solvent using a syringe, a pressure gauge, a tightly fitting removable internal glass liner, and a magnetic stirring bar. Commercially available anhydrous *i*-PrOH was degassed prior to use, by sparging nitrogen for at least 30 minutes. A commercially available 1.0M solution of *t*-BuOK in *t*-BuOH was used following degassing.

The catalyst (0.01 mmol) and imine substrate (1 mmol) were placed in the vessel, which was purged with nitrogen and then with hydrogen at least three times, by pressurising to 5 bar and releasing the pressure. *i*-PrOH (4 mL) was added and the reaction was purged three times with hydrogen. A solution of *t*-BuOK in *t*-BuOH (1.0 M, 1.0 mL, 1.0 mmol) was added and the reaction purged a further three times. Finally, the vessel was pressurised to 15 bar of hydrogen and stirred at 50-65°C for 18-21 hours. When the pressure was released, a sample of the crude reaction was analysed (derivatised or underivatised) by chiral GC (DEX-CB column) for conversion and enantiomeric purity. Conversions were also determined using ^{1}H NMR spectroscopy. Liquid imines were added

to the catalyst in the purged vessel as a solution in *i*-PrOH. Variations from this procedure are described in the relevant tables and table footnotes, in the following Examples.

Hydrogenation substrates in the following Examples are either available commercially (Examples 5, 6 and 8) or may be prepared by the reaction of an amine and a ketone in toluene in the presence of 4A molecular sieves (Examples 4 and 7).

Example 4: Hydrogenation of *N*-(1-phenylethylidene)aniline
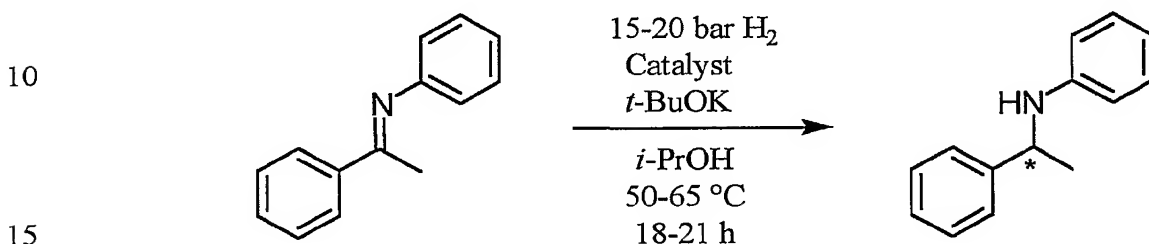
Catalyst	Molar eq. *t*-BuOK	S/C	Conv. (%)	ee (%)
(*S*)-MeO-BIPHEP RuCl₂ (*S,S*)-ANDEN	1	100	17	56
(*R*)-MeO-BIPHEP RuCl₂ (R,R)-DPEN	1	100	98	50
(*R*)-BINAP RuCl₂ (*R,R*)-DPEN	1	100	22	49
(*S*)-Tol-BINAP RuCl₂ (*S,S*)-DPEN	1	100	100	49
(*R,R*)-Me-DuPHOS RuCl₂ (*R,R*)-DPEN	1	100	94	85
(*R,R*)-Me-DuPHOS RuCl₂ (*R,R*)-DPEN	0.5	100	93	84
(*R,R*)-Me-DuPHOS RuCl₂ (*S,S*)-DPEN	1	100	36	16
(*S,S*)-Et-DuPHOS RuCl₂ (*S,S*)-DPEN	1	100	99	91
(*S,S*)-Et-DuPHOS RuCl₂ (*S,S*)-DPEN	0.5	100	99	89
(*S,S*)-Et-DuPHOS RuCl₂ (*R,R*)-DPEN	1	100	60	11
(*S,S*)-*i*-Pr-DuPHOS RuCl₂ (*R,R*)-DPEN	1	100	99	89
(*R,R*)-Et-DuPHOS RuCl₂ (*R,R*)-DACH [a]	0.1	1000	20	88
(*R,R*)-Et-DuPHOS RuCl₂ (*R,R*)-DACH [b]	0.05	1000	97	94

a   [substrate] = 0.5M; 20 hours reaction time
b   [substrate] = 4M; 69 hours reaction time

Example 5: Hydrogenation of 2,3,3-trimethylindolenine
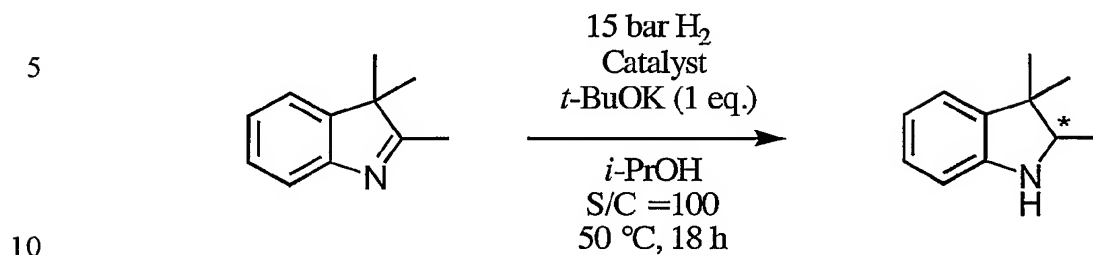
Catalyst	Conv. (%)	ee (%)
(S)-MeO-BIPHEP RuCl₂ (S,S)-ANDEN	30	88
(R)-MeO-BIPHEP RuCl₂ (R,R)-DPEN	71	66
(R)-BINAP RuCl₂ (R,R)-DPEN	81	68
(S)-Tol-BINAP RuCl₂ (S,S)-DPEN	86	67
(S,S)-i-Pr-DuPHOS RuCl₂ (R,R)-DPEN	25	53
(S,S)-Et-DuPHOS RuCl₂ (S,S)-DPEN	64	34
(R,R)-i-Pr-BPE RuCl₂ (S,S)-DPEN	21	37
(S,S)-Et-BPE RuCl₂ (S,S)-DPEN	91	12

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<u>Example 6: Hydrogenation of 2-methylquinoxaline</u>

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15
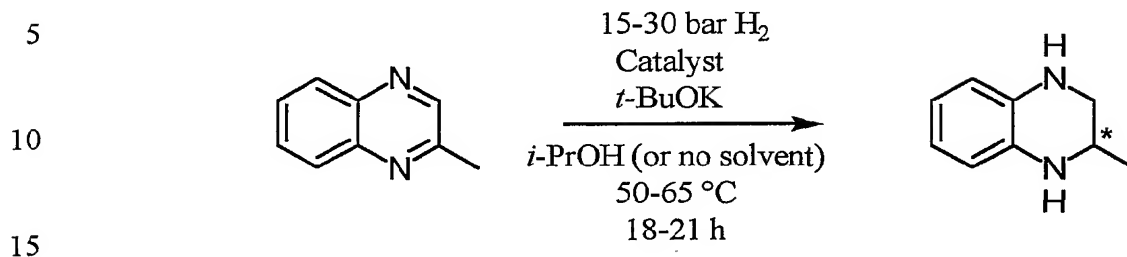
Catalyst	Molar eq. *t*-BuOK	S/C	Conv. (%)	ee (%)
(*S,S*)-Et-BPE RuCl$_2$ (*S,S*)-DPEN	1	100	98	39
(*R,R*)-Me-BPE RuCl$_2$ (*R,R*)-DPEN	1	100	86	29
(*S,S*)-Et-DuPHOS RuCl$_2$ (*S,S*)-DPEN	1	100	95	47
(*R,R*)-Et-DuPHOS RuCl$_2$ (*R,R*)-DACH [a]	0.05	1000	98	40
(*R*)-NORPHOS RuCl$_2$ (*R,R*)-DPEN	1	100	87	14
(*R*)-3,5-Xylyl-Phanephos RuCl$_2$ (*S,S*)-DPEN	1	100	89	45
(*S*)-4-MeO-3,5-Xylyl-Phanephos RuCl$_2$ (*R,R*)-DPEN	1	100	90	66
(*S*)-MeO-BIPHEP RuCl$_2$ (*S,S*)-ANDEN	1	100	61	16
(*R*)-MeO-BIPHEP RuCl$_2$ (*R,R*)-DPEN	1	100	92	41
(*S*)-HexaPHEMP RuCl$_2$ (*S,S*)-DACH [a]	0.05	1000	100	65
(*S*)-HexaPHEMP RuCl$_2$ (*S,S*)-DACH	1	100	94	81
(*S*)-HexaPHEMP RuCl$_2$ (*R,R*)-DACH [a]	0.05	1000	100	69
(*S*)-HexaPHEMP RuCl$_2$ (*S,S*)-DPEN [a]	0.05	1000	100	69
(*S*)-HexaPHEMP RuCl$_2$ (*R,R*)-DPEN [a]	0.05	1000	100	64
(*S*)-BINAP RuCl$_2$ (*S,S*)-DACH [a]	0.05	1000	100	61
(*R*)-BINAP RuCl$_2$ (*S,S*)-DACH [a]	0.05	1000	100	60
(*R*)-BINAP RuCl$_2$ (*R,R*)-DPEN	1	100	87	55
(*R*)-BINAP RuCl$_2$ (*R,R*)-DPEN [a]	0.05	1000	99	66
(*R*)-BINAP RuCl$_2$ (*S,S*)-DPEN [a]	0.05	1000	100	66
(*R*)-BINAP RuCl$_2$ (*R*)-DAIPEN [a]	0.05	1000	94	62
(*S*)-BINAP RuCl$_2$ (*R*)-DAIPEN [a]	0.05	1000	96	37
(*S*)-Tol-BINAP RuCl$_2$ (*S,S*)-DPEN	1	100	92	57
(*S*)-Tol-BINAP RuCl$_2$ (*S,S*)-DPEN [a]	0.05	1000	100	68

a   reaction run neat (no solvent)

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Example 7: Hydrogenation of *N*-(1-phenylethylidene)benzylamine

(*E*:*Z* = 11.4:1.0)

15 bar H$_2$
Catalyst
t-BuOK

i-PrOH
S/C = 100
65 °C, 18-20 h
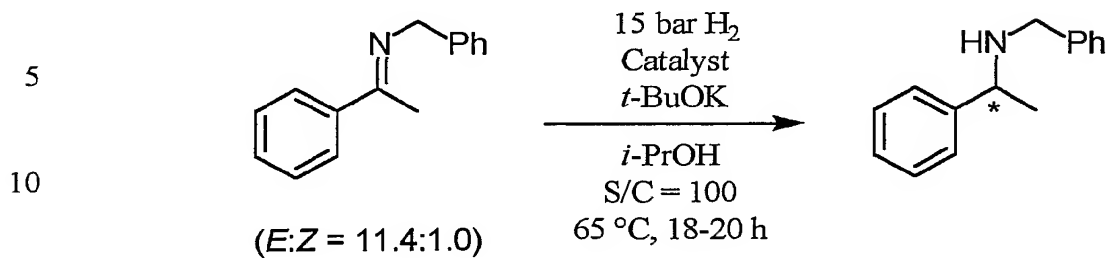
Catalyst	Molar eq. *t*-BuOK	Conv. (%)	ee (%)
(*S*)-Tol-BINAP RuCl$_2$ (*S*,*S*)-DPEN	1	99	28
(*S*)-Tol-BINAP RuCl$_2$ (*S*,*S*)-DPEN	0.05	97	62
(*R*,*R*)-Et-DuPHOS RuCl$_2$ (*R*,*R*)-DPEN	1	100	16
(*R*,*R*)-Et-DuPHOS RuCl$_2$ (*R*,*R*)-DPEN	0.05	99	37

Example 8: Hydrogenation of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline

15 bar H$_2$
Catalyst
t-BuOK (base)

i-PrOH
S/C/base = 100/1/20
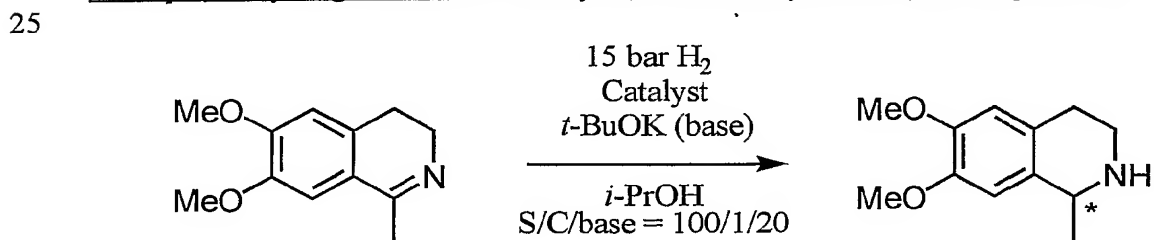
Catalyst	Temp. (°C)	Time (h)	Conv. (%)	ee (%)
(*R*,*R*)-Et-DuPHOS RuCl$_2$ (*R*,*R*)-DACH	65	68.5	79.5	79
(*R*,*R*)-Et-DuPHOS RuCl$_2$ (*R*,*R*)-DACH	80	68.5	96	76

CLAIMS

1.   A process for the preparation of an enantiomerically enriched chiral amine of formula (**10**), or the opposite enantiomer thereof, from an imine of formula (**11**)

$$
R^1 \overset{NHR^3}{\underset{}{\wedge}} R^2 \qquad R^1 \overset{N^{-}R^3}{\underset{}{\wedge}} R^2
$$

(**10**)   (**11**)
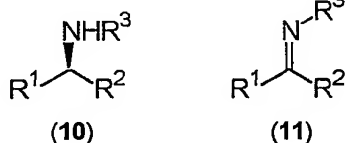
wherein (i) R^1 is aryl, R^2 is alkyl and R^3 is aryl or aryl-CH_2-, or (ii) R^2 is linked with R^1 and/or R^3 to form one or more rings and R^3 or R^1 (if not in a ring) is H or a non-interfering organic group, the number of C atoms in each of R^1, R^2 and R^3 being up to 30, which comprises asymmetric hydrogenation of the imine in the presence of a base and, as catalyst, a ruthenium complex of a chiral diphosphine and a chiral diamine.

2.   A process according to claim 1, wherein R^1 and R^3 are each aryl and R^2 is alkyl, or R^1 and R^2 or R^2 and R^3 are linked to form a cycloalkyl ring having a fused aromatic ring.

3.   A process according to claim 1 or claim 2, wherein R^2 and R^3 are linked, i.e. the imine (**11**) is cyclic.

4.   A process according to any preceding claim, wherein the ruthenium complex is an enantiomerically enriched compound of formula $(DIP)RuX_2(DIA)$, or any of the possible diastereoisomers, in which DIP is a bis-tertiary phosphine in which the two phosphorus atoms are linked by a C_{2-7} carbon chain such that they form a 5-10 membered ring with the Ru atom, X is halide or carboxylate, and DIA is a vicinal diamine with any aromatic, alkyl or hydrogen substituent on the C_2-carbon chain linking the nitrogen atoms.
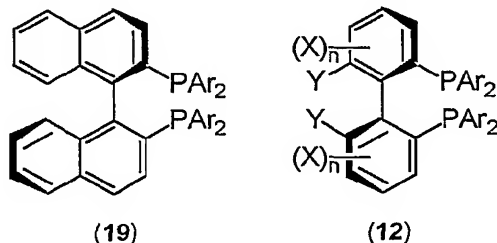
5.   A process according to claim 4, wherein X is Cl, Br, I or F.

6.   A process according to claim 5, wherein X is Cl.

7.   A process according to any of claims 4 to 6, wherein DIP is an atropisomeric bis-tertiary phosphine in which the two phosphorus atoms are linked by a biaryl backbone.

8.   A process according to claim 7, wherein DIP is selected from a binaphthyl ligand of formula (**19**), a biphenyl ligand of formula (**12**), and the opposite enantiomers thereof

(19)   (12)

in which Ar is a phenyl group optionally substituted with up to two alkyl groups, Y is methyl or methoxy and $(X)_n$ represents one or more non-interfering substitutents.
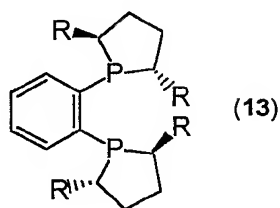
9.   A process according to claim 7 or claim 8, wherein the imine (**11**) is cyclic.

10.   A process according to claim 7 or claim 8, wherein the imine (**11**) is acyclic and R^3 is aryl-CH_2-.

11.   A process according to any of claims 4 to 6, wherein DIP is a ligand in which each P atom forms part of a phospholane ring.

12.   A process according to claim 11, wherein DIP is a DuPHOS ligand of formula (**13**) or the opposite enantiomer thereof

(13)

in which R is C_{1-6} linear or branched alkyl.

13.   A process according to claim 11, wherein DIP is methyl DuPHOS (R = Me) or ethyl DuPHOS (R = Et).

14.   A process according to any of claims 11 to 13, wherein the imine (**11**) is acyclic and R^3 is aryl.

15.   A process according to any of claims 11 to 13, wherein the imine (**11**) is a dihydroisoquinoline.

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16.   A process according to any of claims 4 to 15, wherein DIA is a diamine of general formula (14)
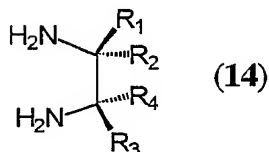
(14)

in which at least one of the amine-bearing centres is stereogenic, R_1, R_2, R_3 and R_4 are independently H, C_{1-20} or C_{6-20} aromatic group, or any pair of R_1, R_2, R_3 and R_4 is linked to form one or more rings.

17.   A process according to claim 16, wherein DIA is selected from the compounds (15) – (19) and the opposite enantiomers thereof

(15): (R,R)-DPEN   (16)   (17): (R)-DAIPEN

(18): (R,R)-ANDEN   (19): (R,R)-DACH
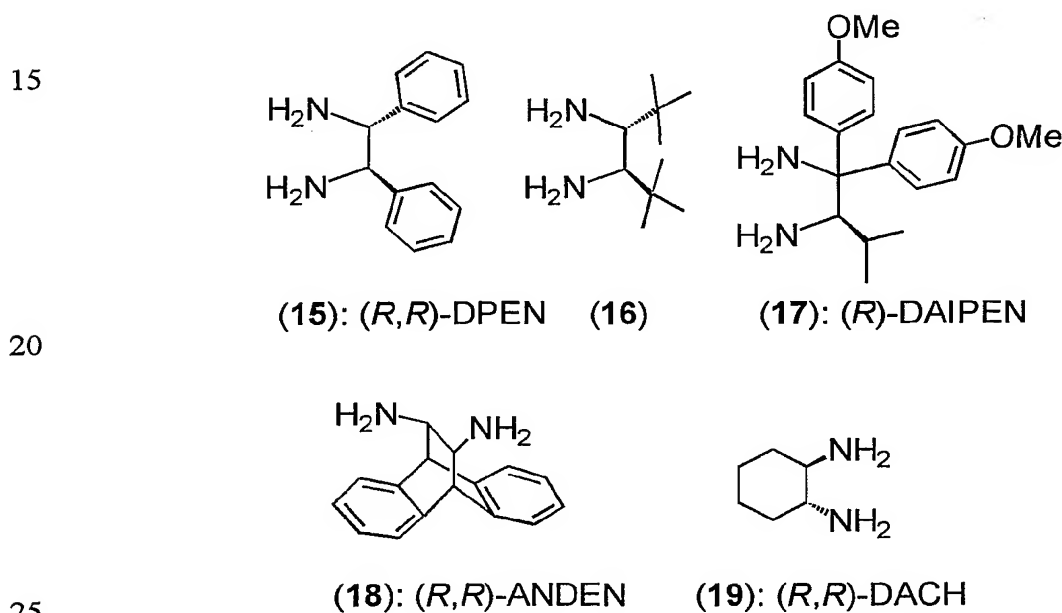
18.   A process according to claim 17, wherein DIA is (R,R)-DPEN and DIP is either (R,R)-methyl DuPHOS or (R,R)-ethyl DuPHOS, or the corresponding process in which a matched pair of (S,S)-stereoisomers is used.

19.   A process according to any preceding claim, wherein the base is present in an amount sufficient to give substrate conversion of at least 80%.

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20.   A process according to claim 19, wherein the amount of the base is in the range of about 0.01-2 molar equivalents relative to the imine (**11**).

21.   A process according to claim 20, wherein R^1 is aryl, R^2 is alkyl and R^3 is aryl-CH_2- and wherein the amount of additional base is about 0.05 equivalents or lower relative to the imine (**11**).

22.   A process according to any of claims 19 to 21, wherein the base is an alkali metal alkoxide.

23.   A process according to claim 22, wherein the base is potassium *tert*-butoxide or sodium isoproproxide.

24.   A process according to any preceding claim, wherein the reaction is conducted in a solvent selected from isopropanol, ethanol, toluene, benzene, chlorobenzene and tetrahydrofuran.

25.   A process according to claim 24, wherein the reaction solvent is isopropanol.

26.   A process according to any of claims 1 to 23, wherein no reaction solvent is used.

27.   A process according to any preceding claim, wherein enantiomeric enrichment of the amine (**10**) is at least 50% ee.

28.   A process according to claim 27, wherein enantiomeric enrichment of the amine (**10**) is at least 80% ee.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   C07C209/52   C07D209/08   C07D241/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7   C07C   C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2001	17/09/2001

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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